be viewed as biases or an expression of true preferences is a matter for further discussion.

HC4

UNDERSTANDING THE PAYER DILEMMA WITH BIOSIMILAR MABS: STRIKING THE RIGHT BALANCE BETWEEN BUDGET NEEDS AND PATIENT OUTCOMES

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OBJECTIVES: The first infliximab biosimilars reached the EU in September 2013, representing the first biosimilar monoclonal antibodies (mAbs) to obtain EMA approval. Although commercialization in the major European markets will only start in February 2015, payers in Nordic and Eastern European countries have already faced the dilemma of striking the balance between potential savings accrued from use of less expensive infliximab biosimilars and demands for robust proof of clinical efficacy and safety. This work identifies payers' evidence expectations, their reliance on regulators' decisions and how potential savings can influence access and recommendations to target patient populations. **METHODS:** Exploratory qualitative primary research with payers (N=12) from France, Italy, Spain, UK, Germany and Netherlands. Collection of data about the current and future attitudes towards biosimilar health technology assessments at the national and, if applicable, local levels will be conducted, as well as perceived price and access trade-offs. **RESULTS:** (1) Payers will mainly defer to the EMA the decision on acceptability of biosimilar indication extrapolation (indications where biosimilars do not have direct clinical trial data); (2) It is understood that mAb biosimilar clinical development is more onerous and costly than small molecule generics, thus payers do not expect the same magnitude of discounts offered vs. originator; (3) Although eager to obtain savings from broad patient populations, payers will not implement pharmacy-level substitution or enforce biosimilar use in originator-experienced patients; (4) Use in naïve patients will be recommended in most markets. **CONCLUSIONS:** Across the EU5, payers acknowledge physicians' concerns over long term safety and efficacy of biosimilars. Nonetheless, they will rely on the regulators evaluations and expert panels to justify implementing recommendations, and in some markets, restrict formularies based exclusively on cost. Moreover, they have conservative discount expectations at launch, with the long-term aim of incentivizing further competition from other biosimilar manufacturers.

RESEARCH ON METHODS – Modeling Studies

MO1

QUASI-MONTE CARLO SIMULATION AND VARIANCE REDUCTION TECHNIQUES SUBSTANTIALLY REDUCE COMPUTATIONAL REQUIREMENTS OF PATIENT-LEVEL SIMULATION MODELS: AN APPLICATION TO A DISCRETE EVENT SIMULATION MODEL

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OBJECTIVES: Patient-level simulation models provide increased flexibility to overcome the limitations of cohort-based approaches in health-economic analysis. However, computational requirements of reaching convergence is a notorious barrier. The objective was to assess the impact of using quasi-monte carlo simulation (QMCS) and variance reduction techniques (VRTs) on computational requirements. **METHODS:** A recently published discrete event simulation model assessing the cost-effectiveness of an adjunctive antipsychotic treatment for depression was used. The following VRTs were implemented: antithetic variables, common random numbers (CRN) and the combination (Anti_CRN). In addition, QMCS was conducted using the Sobol low discrepancy sequence. The minimal number of patients required to reach equal precision as the reference situation of 1,000,000 simple monte carlo simulations (MCS) was recorded. Precision was defined by the standard error (SE) of the incremental net monetary benefit (INMB) at a willingness to pay of €20,000 per quality adjusted life year gained. VRT simulations were replicated 100 times. INMB estimates were compared with the reference situation using mean squared error (MSE), mean absolute error (MAE) and percentage of under- and overestimations. **RESULTS:** Reference INMB (SE) was €1,413 (76). The average number of patients required to reach reference precision were 929,628, 35,692, 41,683 and 36,803 for antithetic variables, CRN, Anti_CRN and Sobol respectively. This implied a computation time reduction ranging between 7% and 96% compared to simple MCS. MSE was 346,036, 16,314, 155,950 and 7,475 respectively. MAE was 588, 105, 387 and 86 respectively. Antithetic variables and Anti_CRN structurally underestimated INMB (99% and 100%). CRN marginally overestimated INMB in 76 replications. **CONCLUSIONS:** QMCS and VRT reduce computational requirements in terms of simulated patients and computational time up to 96%, enhancing the practical feasibility of patient-level simulation models. This particularly applies to Sobol and CRN. Antithetic variables should be used with caution and its structural bias warrants further research.

MO2

TRANSITION PROBABILITY ESTIMATION USING REPEATED SAMPLING FROM A FITTED MIXED MODEL

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OBJECTIVES: Markov model is one of the most used decision analytic models in health care. Transitions between health states in a Markov model is driven by transition probability matrix. When the number of patients and observed transitions are limited, transition probability estimation becomes challenging. The objective of this exercise is to demonstrate how transition probabilities can be estimated by simulating data from a statistical model fitted to patient-level data. **METHODS:** An economic model for ranibizumab in mCNV secondary to pathological myopia (submitted to NICE in June 2013) was adapted for forthcoming Asian reimbursement submissions. BCVA (Best Corrected Visual Acuity) scores were available for limited number of East Asian patients (N=35) from a phase III, 12-month, randomized, double-masked, multicenter, active-controlled study (RADIANCE). To populate a transition probability matrix with 8 health states based on BCVA scores, a statistical model was proposed to simulate a larger hypothetical patient cohort. A mixed-effect model was fitted on the observed BCVA scores with baseline BCVA score as covariate, patients as random effect and an autoregressive AR(1) error correlation structure amongst the repeated observations. This model was used to simulate a patient cohort of 35,000. Transition probabilities were estimated using traditional division by row sum method. Several simulations were run to confirm consistency of results. **RESULTS:** From baseline to month 3, percentage of patients with BCVA $\geq$ 20 letters gain was 22.45% in observed data vs 22.49% in simulated data, and percentage of patients with BCVA $\geq$ 20 letters loss was 0.008% in observed data vs 0.009% in simulated data. BCVA change from baseline to month 3 in simulated data (mean=13.3, SD=8.3) was verified with that of the observed data (mean=13.3, SD=8.8). **CONCLUSIONS:** Transition probability estimation by simulation from a fitted statistical model can overcome the challenges posed by small patient cohorts and multiple state transitions.

MO3

EXTRAPOLATION OF TRIAL-BASED SURVIVAL CURVES USING EXTERNAL INFORMATION

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OBJECTIVES: In cost-effectiveness analysis (CEA), mean survival difference (QALY-adjusted) over a lifetime horizon is required. Parametric models are necessary to extrapolate survival outcomes beyond the Randomized Controlled Trial (RCT) period. However, mean survival is very sensitive to the assumed model and different mean survival times may result from models fitting similarly well to the RCT data. We investigate the idea that other sources of information, external to the trial data, could be used to inform model choice and estimation. **METHODS:** We explored various survival models and we show how external information can be used to put constraints on spline-based survival models. We illustrate with a Technology Appraisal (TA) of head and neck cancer where RCT evidence had 5 year follow up. A US cancer database (SEER), general population data and expert opinion were used to impose constraints on overall survival, conditional survival, and hazard ratio. RCT and external data were fitted simultaneously within a Bayesian framework. **RESULTS:** Standard survival time distributions were insufficiently flexible to simultaneously fit both the RCT data and general population constraints. Spline models were sufficiently flexible, although there were difficulties choosing initial values. A good fit to all sources of internal and external evidence was achieved within one integrated model using splines on the log hazard. Cetuximab in addition to radiotherapy improves the expected survival by 4.7 months [95% CrL: 0.4; 9.1] compared to radiotherapy alone. **CONCLUSIONS:** The method enabled us to estimate models consistent with all evidence. Clinical knowledge is essential to guide the interpretation of the external data sources. The method could be used to analyze other RCTs on other cancers and with other treatments. Other flexible models than splines could be investigated.

MO4

ESTIMATING SURVIVAL DATA FROM PUBLISHED KAPLAN-MEIER CURVES: A COMPARISON OF METHODS

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OBJECTIVES: Health technology assessment of treatments often requires estimates of their survival curves. Individual patient data (IPD) are often unavailable and the survival curves are usually calculated by fitting a nonlinear least squares (NLS) model directly to Kaplan Meier plots provided in the published literature. This method does not account for the uncertainty associated with the Kaplan Meier curve and can lead to biased estimates. Although the IPD are often missing, the Kaplan Meier curve itself can be digitised and used to approximate what the original IPD could have been. **METHODS:** We simulated trial IPD data from different survival distributions in order to assess the accuracy of the IPD reconstruction methods. The assessment of accuracy is made at multiple stages and ultimately the effects on the incremental cost effectiveness ratio (ICER) estimates are compared. To do so, a simple cost-effectiveness model was developed, assuming two health states (alive and dead), and assigning costs (£1,000 per month plus drug costs) and a utility score (0.70) to generate ICERs. Two additional methods to curve fitting are compared against the NLS approach – those suggested by Guyot (G), and by Hoyle & Henley (HH). **RESULTS:** We find that the methods differ in accuracy at each of the following two stages; (a) model selection via the AIC and secondly (b) survival model parameter estimation. When an underlying Weibull function was assumed, the 'true' ICER should be £28,924, compared against £31,182 £33,449 and £31,650 for the NLS, HH and G methods respectively. When an underlying loglogistic function was assumed, the NLS, HH and GG methods produced ICERs of £26,507, £25,559 and £25,857, compared to a 'true' ICER of £25,779. **CONCLUSIONS:** These findings suggest that inherent biases may be apparent in each of the approaches, and these may manifest themselves differently, depending upon the 'true' shape of the underlying data.

QALY-RELATED STUDIES

QA1

ECONOMIC ORPHANS? THE PREVALENCE OF CHILD-SPECIFIC UTILITIES IN NICE APPRAISALS FOR PAEDIATRIC INDICATIONS

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OBJECTIVES: Children have been termed "therapeutic orphans" due to the paucity of age-specific therapeutic data. Here we review the extent to which utility data derived from under-18s were used to inform National Institute for Health and Care Excellence (NICE) Technology Appraisals (TAs) providing cost-effectiveness guidance in paediatric indications, in line with the NICE reference case. **METHODS:** All 311 published TAs up to April 2014 were initially sifted to identify therapeutic recommendations for children. Identified TAs were reviewed to determine if a cost-utility analysis (CUA) was performed. For each CUA, the published TA along with the manufacturer's submission (single TAs) or the assessment report (multiple TAs) were examined to determine the origin of the utilities used. **RESULTS:** Of 35 published TAs reviewed, 27 analysed cost-per-QALY and made recommendations for treatment of under-18s. Of these, 17 used adult utilities, 1 of which attempted to adjust the adult values for children; 3 considered child and adult populations as one, with child-derived data used within the overall model inputs for the whole population, 1 of which adjusted both child and adult utilities by age. Only 6 studies used child-specific utilities: 1 assumed a specified change from treatment on a generic QoL instrument, 2 used parent-reported utilities on a generic QoL instrument, 1 used parent-reported utilities mapped from a disease-specific scale and 2 used child-reported utilities mapped from a disease-specific scale. One MTA contained diverging submissions, 1 adult-derived and 1 child-reported. No trends over time in the types of utilities used were apparent from visual examination of the results. **CONCLUSIONS:** Despite NICE's reference case specifying that utilities should be measured in the population in question, children may also be termed "economic orphans" with the majority of cost-utility submissions applying adult-derived utilities to paediatric indications and no trend away from this apparent over time.

QA2

COST-UTILITY OF CANCER THERAPIES – THE 'COST' OF DIFFERENT UTILITY GENERATION STRATEGIES

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OBJECTIVES: To explore the impact of different utility measurement strategies on the results of a cost-effectiveness analysis, funding decisions, decision uncertainty and value of information. **METHODS:** Data from a UK trial of two cancer therapies (active versus standard care) were analysed using NICE reference case methods. Within-trial, cost-utility analyses were conducted with utility based on a number of strategies: A) Observed EQ-5D; cancer-specific utility based on the EORTC QLQ-C30 B) the EORTC-8D and C) the QLQ_U; Mapping from QLQ-C30 to EQ-5D using an algorithm generated in D) the same cancer patient group and E) a different cancer group. Incremental cost-effectiveness ratios (ICERS) were calculated. Bootstrapped net benefit estimates allowed generation of cost-effectiveness acceptability curves (CEACs) and population expected value of perfect information (EVPI) was calculated using incremental cost scenarios. Results were compared across utility strategies. **RESULTS:** There were small but important differences observed in the incremental QALYs which ranged from 0.067 (EQ-5D) to 0.036 (EORTC-8D). Large differences were observed in the ICERs generated; for strategies A to E these were: £57,513; £106,264; £102,785; £90,049; £78,885. Using an incremental cost scenario of £3,000 only strategy A yielded an ICER <£30,000. At a QALY willingness to pay threshold (WTPT) of £20,000 there was little decision uncertainty. However, assuming WTPT=£50,000, the probability the active treatment was cost-effective ranged 0.34 (EQ-5D) to 0.025 (EORTC-8D). Using this threshold, the population EVPI for the strategies were: £3,597,844; £120,621; £155,858; £354,094; £805,847. **CONCLUSIONS:** Different utility sources can lead to very different estimates of cost-effectiveness and value of further research and change funding decisions. Estimates of cost-effectiveness based on mapping (even when the algorithm appears to perform well) can differ substantively from those based on observed scores. The lowest ICERs were obtained with the EQ-5D but this may not capture side-effects picked up by the cancer-specific utility measures.

QA3

DO NEW CANCER DRUGS OFFER GOOD VALUE FOR MONEY? THE PERSPECTIVE OF ONCOLOGISTS, PAYERS, PATIENTS, AND GENERAL POPULATION

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OBJECTIVES: To analyze oncologists', payers', patients', and general population´ views on the cost and value of new cancer treatments. **METHODS:** An electronic self-administered questionnaire was developed and randomly distributed, to assess participants' attitudes towards new cancer treatment outcomes and costs during reimbursement decisions. Among the questions asked were two hypothetical scenarios. First, participants were asked to indicate the minimum survival benefit that a new treatment, that cost €50,000 more than the standard therapy, should have to be funded by the Spanish National Health System (NHS). Second, participants were requested to state the highest costs to be afforded by the NHS for a medication increasing patient's quality of life (QoL) twofold with no changes in survival. Responses were used to calculate incremental cost-effectiveness ratios (ICER). **RESULTS:** 53 oncologists, 60 patients, 25 payers, and 50 individuals from general population answered the questionnaire. The minimum improvement median in patient survival that justified the inclusion into the NHS was 5.66 months for oncologists, 8.16 for patients, 9.08 for general population and 10.44 for payers; implying different ICER for oncologists (€106,000/QALY), patients (€73,520/QALY), general population (€66,074/QALY) and payers (€57,471/QALY). The cost stated in QoL-enhancing scenario was €33,167 for patients, €30,200 for general population, €26,000 for oncologists and €17,040 for payers; resulting in ICERs of €82,917/QALY for patients, €75,500/QALY for general population, €65,000/QALY for oncologists, and €42,600/QALY for payers. **CONCLUSIONS:** All the estimated ICER values were higher than the thresholds usually described in the literature (€20,000-30,000/QALY), with relevant differences among the groups. In both scenarios, payers were less prone to pay for therapeutic improvements compared to the rest of the participants. On the other hand, oncologists were the ones that most valued gains in survival for a new treatment while patients assigned a higher value for money to a treatment that enhanced the quality of life.

QA4

REIMBURSEMENT DECISIONS FOR PHARMACEUTICALS IN SWEDEN: THE IMPACT OF COST-EFFECTIVENESS AND DISEASE SEVERITY

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OBJECTIVES: The purpose of this study is to evaluate the impact of cost-effectiveness and disease severity on the drug reimbursement decisions made by the reimbursement agency TLV in Sweden. **METHODS:** Cost-effectiveness is measured through the continuous variable cost per QALY, while disease severity is measured by a dichotomous variable indicating high- or not high disease severity. We analyze all reimbursement decisions from 2005 through 2011 where there is data available on cost per QALY and disease severity. Logistic regressions are used to evaluate the impact of cost-effectiveness and disease severity on the drug reimbursement decisions. **RESULTS:** There are 102 decisions with the required data available, 86 where reimbursement was granted and 16 where reimbursement was denied. The median cost per QALY for the drugs that were granted reimbursement was 39 000 euro (9sek/euro), ranging from a negative cost per QALY (better and cheaper) to 136 000 euro. The median cost per QALY for the drugs that were denied reimbursement was 111 000 euro, ranging from 78 000 euro to 1 111 000 euro. The results from the logistic regression analysis show that both the cost per QALY and the level of disease severity are statistically significantly related to the probability of a drug being granted reimbursement. When the cost per QALY exceeds 56 000 euro for non-severe diseases, and 92 000 euro for severe diseases, the probability that reimbursement is denied is higher than the probability that reimbursement is granted. **CONCLUSIONS:** In Sweden, it is sometimes stated as a rule of thumb that 55 000 euro per QALY is a threshold for cost-effective interventions. Our model shows that at this cost-effectiveness ratio, the probability of a new drug becoming reimbursed is 91 % or 98 %, depending on disease severity.

RESEARCH PODIUM PRESENTATIONS – SESSION II

CARDIOVASCULAR DISEASE RESEARCH STUDIES

CV1

THE IMPORTANCE OF TREATMENT CLASSIFICATIONS THAT ACCOUNT FOR CONCOMITANT TREATMENTS IN THE CONTEXT OF A NETWORK META-ANALYSIS COMPARING PHARMACOLOGICAL TREATMENTS FOR CHRONIC HEART FAILURE

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OBJECTIVES: The aim of the study was to assess the comparative efficacy of recommended treatment for chronic heart failure with reduced ejection fraction in terms of all-cause mortality based on a network met-analysis (NMA) of randomized controlled trials (RCTs) and to explore the impact of alternative treatment classifications depending on concomitant treatments. **METHODS:** A systematic literature search identified 56 relevant RCTs (1980-2013) that reported mortality data that were synthesized using a Bayesian Poisson regression NMA model. Treatments were classified as angiotensin converting enzyme inhibitors (ACEI), beta-blockers (BB), angiotensin II receptor blockers (ARB), mineralocorticoid/aldosterone receptor antagonists (MRA) and the $I_f$channel inhibitor (IF) ivabradine. Analysis 1 classified treatments according to the main drugs of interest, whereas Analysis 2 defined treatments according to the main drugs of interest as well as the concomitant treatments belonging to classes of interest if more than 50% of patients were taking concomitant drugs. **RESULTS:** Six regimens were compared in Analysis 1 and 10 regimens were compared in Analysis 2. Analysis 1 resulted in the following rate ratios (RR) versus placebo: ACEI: 0.81 (95% Credible Interval 0.61, 0.95); BB: 0.71 (0.60, 0.80); ARB: 0.90 (0.75, 1.02); ACEI+BB: 0.48 (0.30, 0.76). Analysis 2 resulted in the following RRs versus placebo: ACEI: 0.81 (0.68, 0.95); BB: 0.57 (0.35, 0.87); ARB: 0.81 (0.61, 1.01); ACEI+BB: 0.61 (0.54, 0.68). The treatments that are expected to be most efficacious depended on the treatment classification: Analysis 1 supported ACEI+BB and BB, whereas Analysis 2 supported ACEI+BB+MRA+IF and ACEI+BB+MRA [RR: 0.44 (0.34, 0.58) and 0.48 (0.38, 0.60), respectively]. **CONCLUSIONS:** Combination treatments were likely to be more efficacious than monotherapy and adding a class to a regimen was likely to make it more efficacious regardless of the approach. However, treatment classifications affect the results and interpretation. The approach that accounts for concomitant treatments is preferred.

CV2

WORK PRODUCTIVITY LOSS AND INDIRECT COSTS ASSOCIATED WITH NEW CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS WITH HYPERLIPIDEMIA - ESTIMATES FROM POPULATION-BASED REGISTER DATA IN SWEDEN

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